Article 34 Amendment

Dated: February 28, 2005

WRITTEN AMENDMENT

(Amendment under the provision of Law Section 11)

Commissioner of the Patent Office: Mr.

1. Indication of International Application:

PCT/JP2004/011006

2. Applicant:

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4. Subject of the Amendment:

(1) Description

(2) Claims

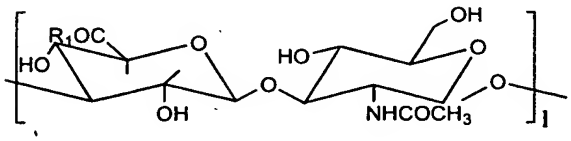
(propylene glycol) and poly(ethylene glycol) is preferable." to "The polyalkylene oxide which is used in the invention is (1) polypropylene glycol or (2) a copolymer comprising poly-(propylene glycol) and poly(ethylene glycol).".

(3) Page 5, line 3 of the description (corresponding to page 7, lines 23 to 24 of the translation), amend "from about 1×10^5 to 1×10^7 daltons" to "from about 1×10^5 to 1×10^7".

(4) Page 5, line 8 to page 6, line 8 of the description (corresponding to page 8, line 5 to page 9, line 14 of the translation), delete "In the case of --- glycol)/poly(ethylene glycol) butoxide."

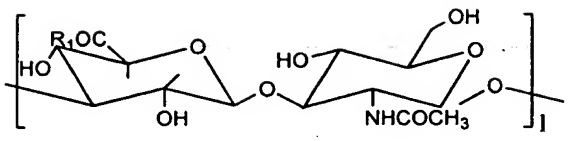
(5) Page 6, line 12 of the description (corresponding to page 9, line 21 of the translation), amend "In the case of using a copolymer" to "In the copolymer".

(6) Claim 1 (corresponding claim 1 of page 18 of the translation), amend the chemical formula (1) from "



R_1 : OH , $-R_2-\underset{\underset{R_3}{|}}{CH}CH_2(OR_4)_mOR_5$ (1)

(wherein R_2 represents NH or O; R_3 represents H or CH_3; R_4 represents C_2H_4 or $CH_2CH(CH_3)$; R_5 represents any one of H, CH_3, C_2H_5, and C_4H_9; l represents an integer of from 300 to 30,000; and m represents an integer of from 3 to 140.)" to "



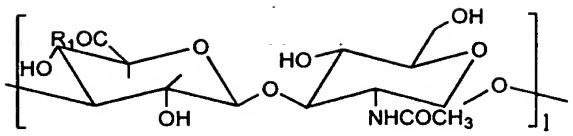
(1)

wherein R_1 represents OH, OM (wherein M represents an alkali metal), or a residue of a polyalkylene oxide derivative which is polypropylene glycol or a copolymer of poly(propylene glycol) and poly(ethylene glycol); and l represents an integer of from 300 to 30,000.".

6. List of Attached Documents:

(1) Page 4, page 5 and page 6 of the description (corresponding to new pages 6 to 8 and new pages 9 to 10 of the translation) (each one copy)

(2) Page 11 of the claims (corresponding new page 18 of the translation) (each one copy)



(1)

wherein R_1 represents OH, OM (wherein M represents an alkali metal), or a residue of a polyalkylene oxide derivative which is polypropylene glycol or a copolymer of poly(propylene glycol) and poly(ethylene glycol); l represents an integer of from 300 to 30,000; and m represents an integer of from 3 to 140.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a phase transition behavior graph of a compound in which JEFFAMINE (registered trademark) XTJ-507 is introduced in an amount of 10 equivalents in terms of hyaluron per 100 equivalents of the carboxyl group of a hyaluronic acid.

Fig. 2 is a phase transition behavior graph of a compound in which JEFFAMINE (registered trademark) XTJ-507 is introduced in an amount of 50 equivalents in terms of hyaluron per 100 equivalents of the carboxyl group of a hyaluronic acid.

Fig. 3 is a phase transition behavior graph of a compound in which JEFFAMINE (registered trademark) XTJ-507 is introduced in an amount of 100 equivalents in terms of hyaluron per 100 equivalents of the carboxyl group of a hyaluronic acid.

Fig. 4 is a phase transition behavior graph of sodium hyaluronate.

Fig. 5 is a phase transition behavior graph of propyl hyaluronate.

BEST MODE FOR CARRYING OUT THE INVENTION

The invention will be hereunder described in detail. Incidentally, these Examples and the like and the description merely exemplify the invention but do not limit the scope of the invention. Needless to say, other embodiments fall within the scope of the invention so far as they coincide with the gist of the invention.

As the hyaluronic acid which is used in the invention, both one which is extracted from animal tissues and one which is produced by a fermentation method can be used. A strain to be used in the fermentation method is a microorganism having a hyaluronic acid producing ability of the *Streptococcus* genus, and examples thereof include *Streptococcus equi* FM-100 (JP-A-63-123392) and *Streptococcus equi* FM-300 (JP-A-2-234689). Materials obtained by cultivation and purification using these variable strains are used. Furthermore, with respect to the molecular weight of the hyaluronic acid, ones having from about 1×10^5 to 1×10^7 are preferable. Incidentally, the hyaluronic acid as referred to in the invention also include alkali metal salts thereof, for example, salts of sodium, potassium, and lithium.

The polyalkylene oxide which is used in the invention

is (1) polypropylene glycol or (2) a copolymer comprising poly-(propylene glycol) and poly(ethylene glycol).

The molecular weight of the foregoing polyalkylene oxide derivative is preferably from 200 to 6,000. When the molecular weight is not more than 200, a reaction product with the hyaluronic acid does not exhibit temperature responsibility. Also, when the molecular weight is 6,000 or more, a precipitate is generated so that a hydrogel is not formed.

In the copolymer comprising poly(propylene glycol) and poly(ethylene glycol), a copolymerization ratio of poly(propylene glycol) to poly(ethylene glycol) is preferably from 1/99 to 99.9/0.1, and more preferably from 20/80 to 99.9/0.1. When the copolymerization ratio falls outside the foregoing range, a reaction product with the hyaluronic acid does not exhibit temperature responsibility.

The content of the polyalkylene oxide derivative is preferably from 5 to 100 equivalents per 100 equivalents of the carboxyl group of the hyaluronic acid. When the content is not more than 5 equivalents, a reaction product with the hyaluronic acid does not exhibit temperature responsibility.

A typical reaction method between the hyaluronic acid and the polyalkylene oxide derivative includes the following two methods.

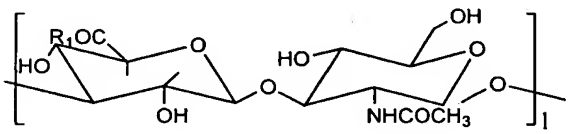
(I) Amide bonding:

Sodium hyaluronate is dissolved in a tetrahydrofuran/water mixed solvent, to which is then added a 1-aminopolyalkylene oxide. 0.1 M HCl and 0.1M NaOH are added

to adjust at a pH 6.8, and 1-ethyl-3-[3-(dimethylamino)-propyl]-carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) are then added. After stirring overnight, the reaction mixture is purified by dialysis and subjected to freeze-drying to obtain a target compound.

CLAIMS

1. (Amended) A compound comprising a hyaluronic acid and a polyalkylene oxide derivative, represented by the following general formula (1), wherein the content of the polyalkylene oxide derivative residue in R_1 is from 5 to 100 equivalents per 100 equivalents of the carboxyl group of the hyaluronic acid:



(1)

wherein R_1 represents OH, OM (wherein M represents an alkali metal), or a residue of a polyalkylene oxide derivative which is polypropylene glycol or a copolymer of poly(propylene glycol) and poly(ethylene glycol); and l represents an integer of from 300 to 30,000.

2. A hydrogel comprising the compound according to claim 1.